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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/797,822	03/09/2004	Chin-Tarng Lin	P/741-178	6560

2352 7590 04/20/2005

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/797,822	LIN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-10 are pending in the application. Claims 1-10 are currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing proliferation of nasopharyngeal cells *in vitro* after administration of an antisense targeted to a gene encoding nucleolin and for reduction of nasopharyngeal tumor cells, implanted in SCID mice, by intravenous administration of an antisense oligonucleotide targeted to a gene encoding nucleolin, does not reasonably provide enablement for proliferation inhibition of any tumor cell or tissue, namely ovarian, colon, oral, uterin, cervical, pulmonary, prostate or leukemia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims

The instant claims are drawn to a therapeutic composition comprising an antisense oligonucleotide (SEQ ID NO:1) and a pharmaceutically acceptable carrier or diluent. The claims further recite a method for proliferation inhibition of tumor cells wherein the antisense

oligonucleotide hybridizes to nucleolin mRNA and inhibits expression of nucleolin and further inhibits proliferation of tumor cells.

The specification as filed discloses inhibition of proliferation of nasopharyngeal cells, *in vitro,* by administration of an antisense targeted to a nucleic acid gene encoding nasopharyngeal (see Figure 3). Further, the specification as filed discloses a reduction of nasopharyngeal tumor cells, in vivo, by intravenous administration of an antisense oligonucleotide targeted to a gene encoding nucleolin (see paragraph 0043). The specification as filed does not teach that because of administration of an antisense compound targeted to nucleolin, nucleolin expression is inhibited and inhibition of proliferation of any tumor cell or tissue, namely ovarian, colon, oral, uterin, cervical, pulmonary, prostate or leukemia, *in vivo* in any animal

There is no guidance in the specification as filed that teaches how to target the claimed antisense compound to human cells or tissues, inhibit the expression of nucleolin *in vivo*, and further provide treatment of tumor cells. Although the specification discloses inhibition of nucleolin mRNA *in vitro* by administration of antisense compound, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claims 1-10 encompass methods of inhibiting a broad range of cancer cells or tissues by use of an antisense targeted to nucleolin gene *in vivo*. Although the specification teaches inhibition of nasopharyngeal cells, *in vitro,* after treatment with an antisense compound (see Figure 3), this guidance is not sufficient to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the instantly claimed methods.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense compounds. Branch stresses that "because it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells" (TIB 23: 45-50 1998). Green *et al.* states that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects" (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2).

The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen *et al.*, who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery....presently, some success has been achieved in tissue

culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen *et al.* concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column)."

Schiavone et al. (Current Pharmaceutical Design, 2004, Vol. 10: 769-784) states "[d]espite promising futures, antisense-based therapeutics are far from being an established reality" (see page 769, abstract). Schiavone et al. further states that "[d]espite the success obtained in *in vitro* studies, the development of antisense drugs has met obstacles in the clinical field where results are far from satisfactory" (see page 780, column 1).

As outlined above, it is well known that there is a high level of unpredictability in the antisense art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely inhibition of proliferation of any tumor cells, by intravenous administration of an antisense oligonucleotide targeted to a gene encoding nucleolin.

While one skilled in the art may be able to find an antisense oligonucleotide targeted to a gene encoding nucleolin and demonstrate inhibition of nucleolin in nasopharyngeal cells *in vitro* after treatment with the antisense oligonucleotide or inhibition of proliferation of nasopharyngeal cells implanted in SCID mice, the specification as filed does not teach how to administer any antisense oligonucleotide to any tumor cell or tissue and further to inhibit proliferation of any tumor cell or tissue by administration of the antisense compound targeted to nucleolin, as claimed.

Crooke (Antisense Research and Application, Chapter 1, Springer-Verlag, New York. 1998) supports the difficulties of extrapolating from in vitro experiments and states on p. 3, paragraph 2, "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]."

Further, Crooke (Oncogene 2000, Vol. 19: 6651-6659) outlines the problems with human tumor zenograft models by stating that "...it is feasible to reduce target RNA and ... antiproliferative effects in some of these models.... However, the doses required to produce such effects have typically been greater than those required to produce effects in several organs.... Moreover, although positive results have been reproducible, the variability observed in these models has been significantly greater than other animal models. At least some of the discrepancies appear to derive from a failure of these agents to distribute broadly in human tumor zenografts." (See page 6655, column 1). Crooke further points out that a "... uniquely challenging consideration for antisense inhibitors of genes thought to be involved in the proliferation of malignant cells, is proof of mechanism.... Simply demonstrating (or failing to demonstrate) a change in the level of a target in a proliferative cell population is inadequate information to support firm conclusions about mechanism." (See page 6655, column 2).

In view of the unpredictability in the art of antisense-based therapy, as outlined above, and the unpredictability of applicant's human tumor zenograft model, the specification as filed

does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation.

Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of a target gene. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the antisense molecule *in vivo*, delivery of the antisense molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al. (U.S. Patent No. 6,165,786).

The instant claims are drawn to an antisense oligonucleotide targeted to nucleolin mRNA and suppress nucleolin expression. The claims are further drawn to an antisense oligonucleotide (SEQ ID NO:1) wherein the antisense is effective in inhibition of tumor cell proliferation,

effective in reduction of tumor size in vivo and the antisense is a phosphorothioate-modified oligonucleotide and the antisense is in a vector and is in a therapeutic composition comprising a pharmaceutically acceptable carrier. The claims recite the nucleolin mRNA comprises a translation start codon.

Bennett et al. teach an antisense oligonucleotide identical to SEQ ID NO:1 of the instant claims (see column 55, line 20) and wherein the nucleotide sequence can hybridize to nucleolin mRNa and specifically suppress nucleolin expression (see column 3, lines 1-26). Bennett et al. further teach the mRNA target comprise a translation start codon (see column 3, lines 40-45) and the antisense is a phosphorothioate-modified oligonucleotide (see column 6, lines 24-37).

Thus, Bennett et al. anticipates claims 1-8 of the instant application.

Claims 1-3 is rejected under 35 U.S.C. 102(b) as being anticipated by NIH-MGC (National Institute of Health, Mammalian Gene Collection 1999, Accession BI752549).

The instant claims are drawn to an antisense oligonucleotide (SEQ ID NO:1) targeted to nucleolin mRNA and suppress nucleolin expression.

NIH-MGC teach an oligonucleotide comprising SEQ ID NO:1. Since the structure of the claimed oligonucleotide was taught by NIH-MBC, the claimed functions "for proliferation inhibition of tumor cells" and "wherein the nucleolin antisense is effective in reduction of tumor size *in vivo*" would have been an inherent property of the oligonucleotide taught by NIH-MGC. Note MPEP 2112.01 states in part "...[w]here the claimed and prior art products are identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established."

Thus, NIH-MGC anticipates claim 1 of the instant application.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as

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Kimberly Chong
Examiner
Art Unit 1635

SEAN McGARRY
PRIMARY EXAMINER
1635